Subclinical Leaflet Thrombosis in Surgical and Transcatheter Bioprosthetic Aortic Valves

Results from RESOLVE and SAVORY registries

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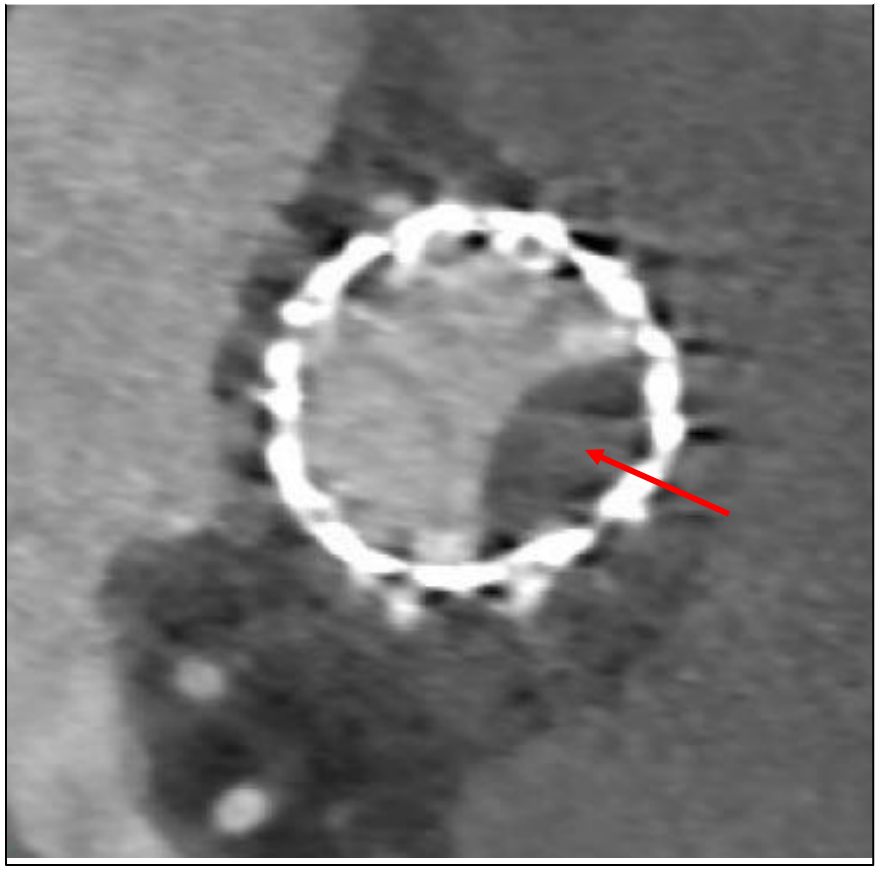
On Behalf of RESOLVE and SAVORY Investigators

Disclosures

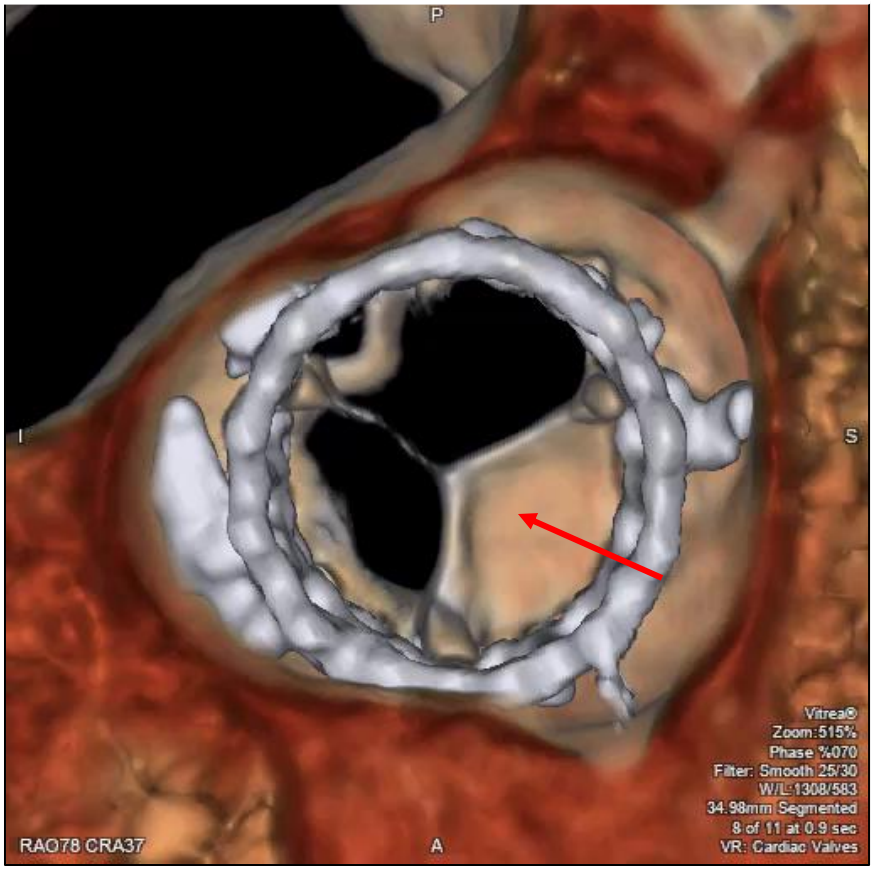
Consulting fee and research grants from Edwards LifeSciences, St. Jude Medical and Medtronic

4D-CT Angiogram of Bioprosthetic Aortic Valve

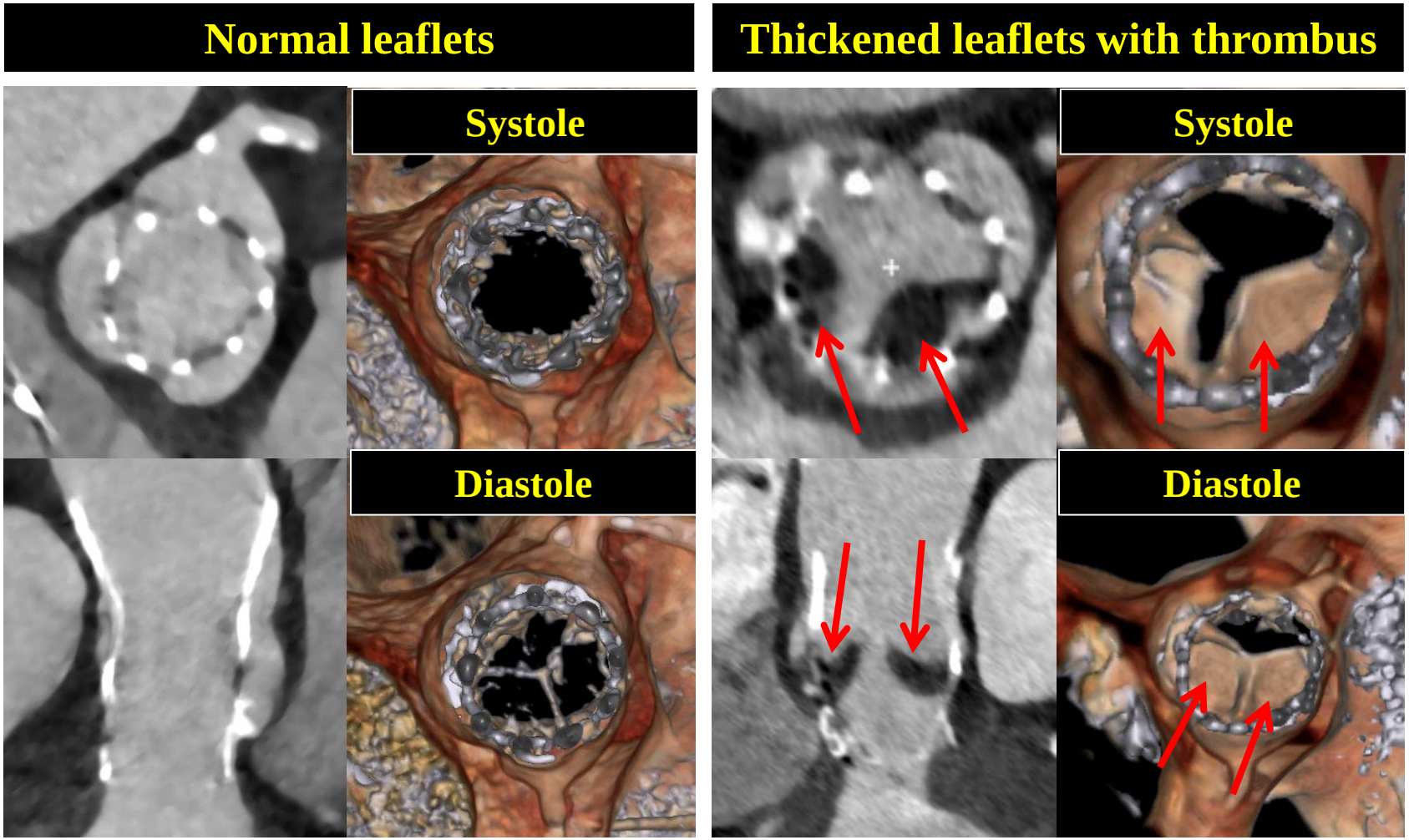
Hypoattenuating opacity



Reduced leaflet motion



Volume rendered CT images of bioprosthetic valves



Makkar R. et al. NEJM 2015

Background

- Subclinical leaflet thrombosis, presenting as reduced leaflet motion on CT, associated with hypoattenuating leaflet thickening
  - Is reported in 10-15% of patients after TAVR.
  - Is noted in both transcatheter and surgical bioprosthetic aortic valves.
  - Is less common in patients on therapeutic anticoagulation with warfarin and resolves with initiation of warfarin.
- However, there are no data on differences between surgical and transcatheter aortic valves, impact of NOACs on the prevention and treatment of this finding, and limited data on valve hemodynamics and clinical outcomes.

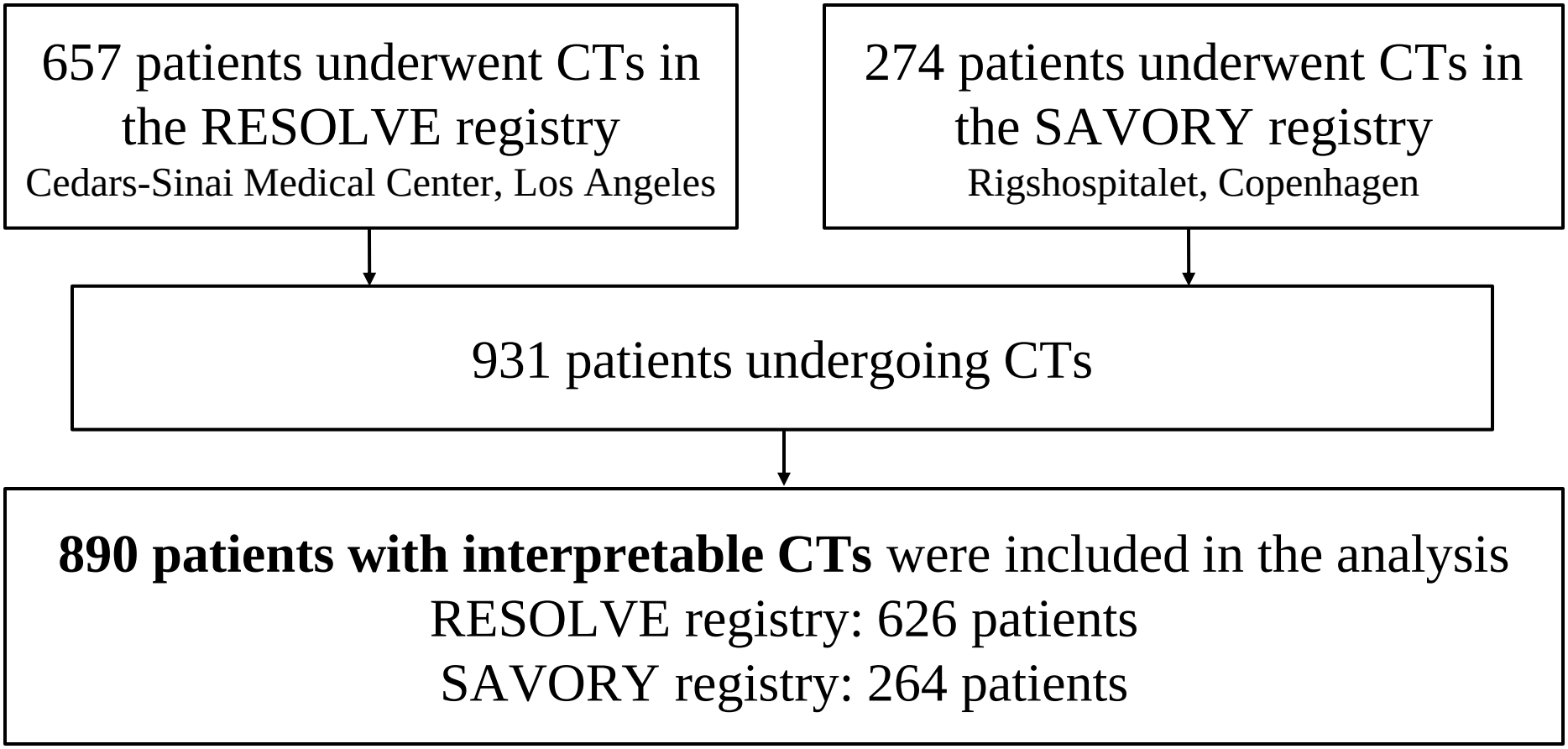
Makkar R. et al. NEJM 2015; Pache G. et al. EHJ 2015; Yanagisawa R. et al. JACC: Cardiovascular Interventions 2016; Hansson NC. et al. JACC 2016; Ruile P. et al. Clin Res Cardiol 2017

Study Objectives

To study subclinical leaflet thrombosis of bioprosthetic aortic valves in terms of

- Prevalence in a large heterogenous cohort of patients
- Differences in TAVR and SAVR
- Impact of novel-oral anticoagulants (NOACs)
- Impact on valve hemodynamics
- Impact on clinical outcomes

Study design



Valve types and timing of CT

Time from TAVR to CT vs. SAVR to CT: p<0.0001

890 patients with interpretable CTs
Median time from AVR to CT 83 days (IQR 32-281 days)

752 transcatheter valves
Median time from TAVR to CT
58 days (IQR 32–236 days)

138 surgical valves
Median time from SAVR to CT
162 days (IQR 79–417 days)

CT Imaging and Evaluation

- All CTs were analyzed at Cedars-Sinai Heart Institute in a blinded manner by a dedicated CT core laboratory.

- Hypoattenuated leaflet thickening of the valve leaflets was assessed using 2D (axial cross-section assessment) and 3D-VR (volume rendered) imaging. Leaflet motion was assessed using four-dimensional volume-rendered imaging.

- Quantification of reduced leaflet motion was based on analysis of a volume-rendered *en-face* image of the aortic valve prosthesis at maximal leaflet opening.

- Reduced leaflet motion was defined as the presence of at least 50% restriction of leaflet motion.

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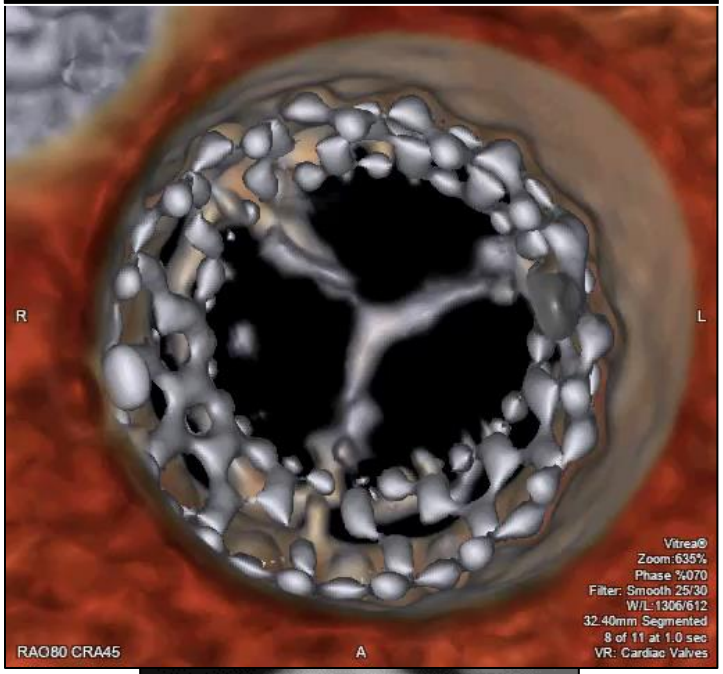
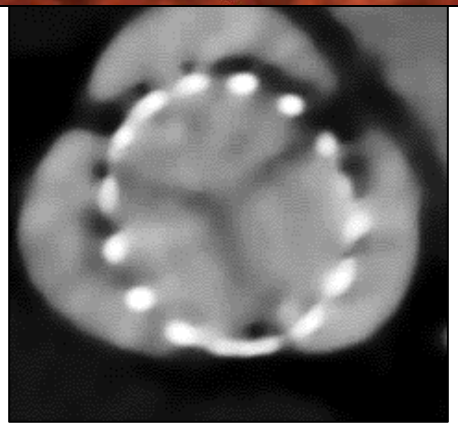
Normal leaflet motion



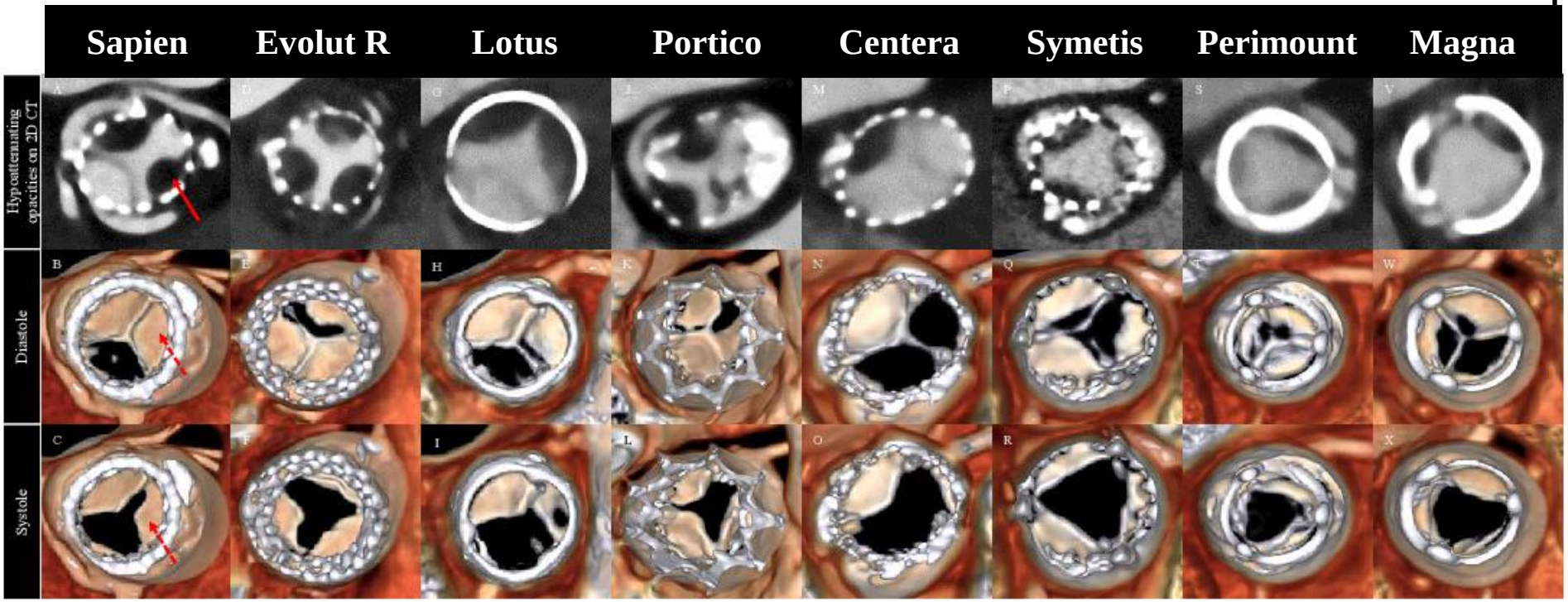


Reduced leaflet motion

Study methodology

- All echocardiograms were analyzed in a blinded manner.
- Data on the antiplatelet and antithrombotic therapy were collected on all clinic visits.
- Clinical follow-up was obtained in all patients for death, myocardial infarction (MI), stroke and transient ischemic attack (TIA).
- All neurologic events, including strokes and TIAs, were adjudicated in a blinded manner by a stroke neurologist.

Reduced leaflet motion in multiple valve types



Prevalence of reduced leaflet motion

Transcatheter vs. surgical bioprosthetic aortic valves: p=0.001

Reduced leaflet motion was present in 106 (11.9%) patients

Transcatheter valves
13.4% (101 out of 752)

Surgical valves
3.6% (5 out of 138)

Baseline characteristics

Patients with and without reduced leaflet motion

Characteristic	Normal leaflet motion (N=784)	Reduced leaflet motion (N=106)	p-value
Age (years)	78·9±9·0	82·0±8·7	0·0009
Male sex	437 (55·7%)	64 (60·4%)	0·37
Medical condition			
Chronic kidney disease	74 (10·2%)	14 (14·3%)	0·22
Hemodialysis	8 (1·2%)	1 (1·0%)	>0·99
Hypercoagulable disorder	9 (1·4%)	0 (0%)	0·61
Hypertension	679 (86·7%)	88 (83·0%)	0·30
Prior stroke	63 (8·1%)	9 (8·5%)	0·88
Prior transient ischemic attack	36 (4·6%)	6 (5·7%)	0·63
Hyperlipidemia	599 (76·6%)	78 (73·6%)	0·49
Diabetes	193 (24·7%)	22 (20·8%)	0·38
PCI within 3 months prior to AVR	84 (10·8%)	13 (12·5%)	0·60
Congestive heart failure	588 (75·3%)	84 (79·3%)	0·37
Syncope	47 (6·1%)	3 (2·9%)	0·26
Atrial fibrillation	233 (29·9%)	17 (16·0%)	0·003
Baseline echocardiogram			
Ejection fraction (%)	57·9±12·6	55·5±13·2	0·07
Mean aortic valve gradient (mmHg)	44·2±13·8	44·6±16·1	0·83
Peak aortic valve gradient (mmHg)	74·2±22·1	73·6±26·2	0·79
Dimensionless index	0·23±0·09	0·22±0·07	0·27

Data are mean ± SD or n(%)

AVR=Aortic valve replacement

Baseline characteristics

Patients with surgical and transcatheter aortic valves

Characteristic	SAVR (N=138)	TAVR (N=752)	p-value
Age-year	71·9±8·6	80·7±8·4	<0·0001
Male sex-no. (%)	88 (63·8%)	413 (54·9%)	0·05
Medical condition - no. (%)			
Chronic kidney disease	6 (4·8%)	82 (11·7%)	0·02
Hemodialysis	0 (0%)	9 (1·3%)	0·23
Hypercoagulable disorder	0 (0%)	9 (1·4%)	0·61
Hypertension	101 (73·2%)	666 (88·7%)	<0·0001
Prior stroke	9 (6·6%)	63 (8·4%)	0·47
Prior transient ischemic attack	3 (2·2%)	39 (5·2%)	0·19
Hyperlipidemia	93 (67·9%)	584 (77·8%)	0·01
Diabetes	28 (20·3%)	187 (24·9%)	0·25
PCI within 3 months prior to AVR	7 (5·2%)	90 (12·0%)	0·02
Congestive heart failure	68 (49·3%)	604 (80·6%)	<0·0001
Syncope	2 (1·5%)	48 (6·4%)	0·02
Atrial fibrillation	31 (22·6%)	219 (29·2%)	0·11
Baseline echocardiogram			
Ejection fraction - %	57·2±11·5	57·7±12·9	0·30
Mean aortic valve gradient - mmHg	43·6±14·4	44·4±14·1	0·91
Peak aortic valve gradient - mmHg	72·5±22·3	74·4±22·7	0·82
VTI ratio	0·26±0·12	0·23±0·08	0·04
Anticoagulation at the time of discharge	31 (22·5%)	187 (24·9%)	0·54
Anticoagulation at the time of CT	38 (27·5%)	186 (24·7%)	0·49
Timing from AVR to CT	162·5 days (80 – 417 days)	58 days (32 – 235 days)	<0·0001
0-6 months	74 (53·6%)	520 (69·2%)	
6-12 months	26 (18·8%)	84 (11·2%)	
>12 months	38 (27·5%)	148 (19·7%)	

AVR=Aortic valve replacement; CT=computed tomogram

Data are mean ± standard deviation or median (interquartile range) for continuous variables; N (%) for categorical variables

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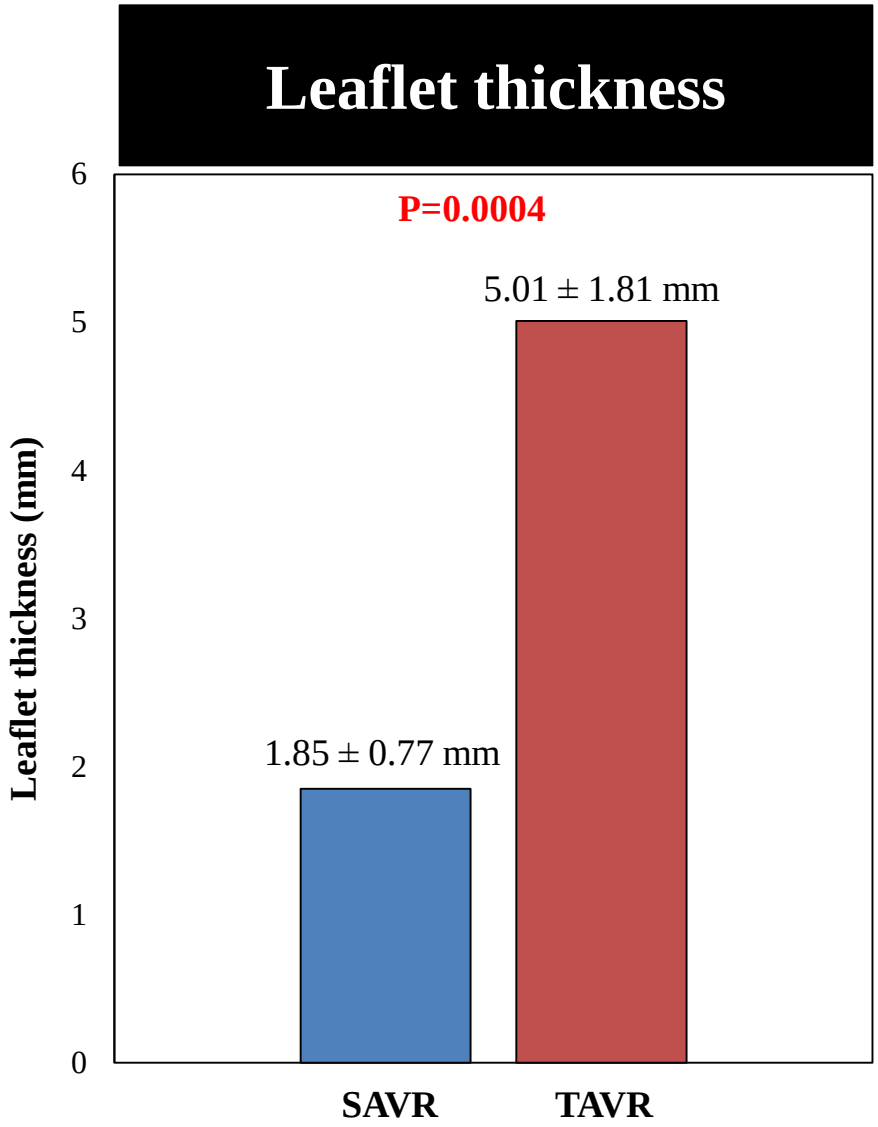
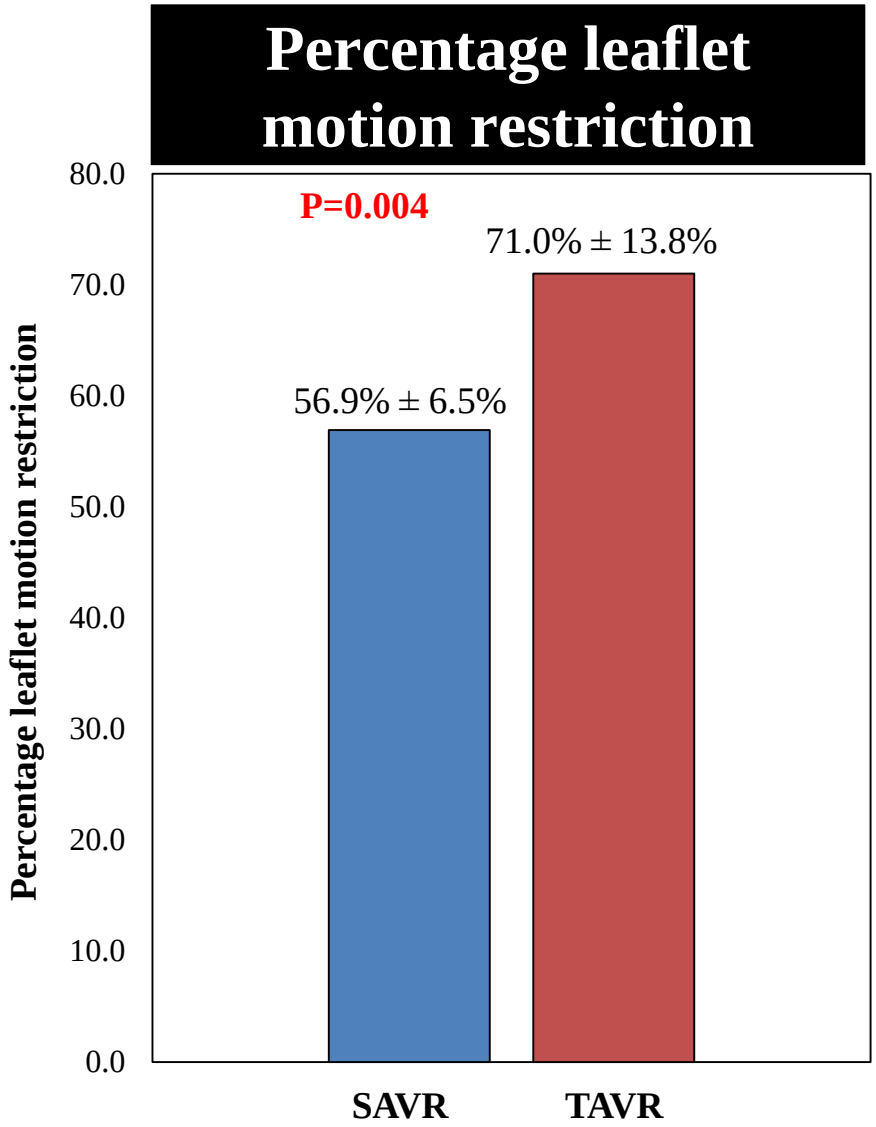
Severity of reduced leaflet motion

Surgical vs. transcatheter valves





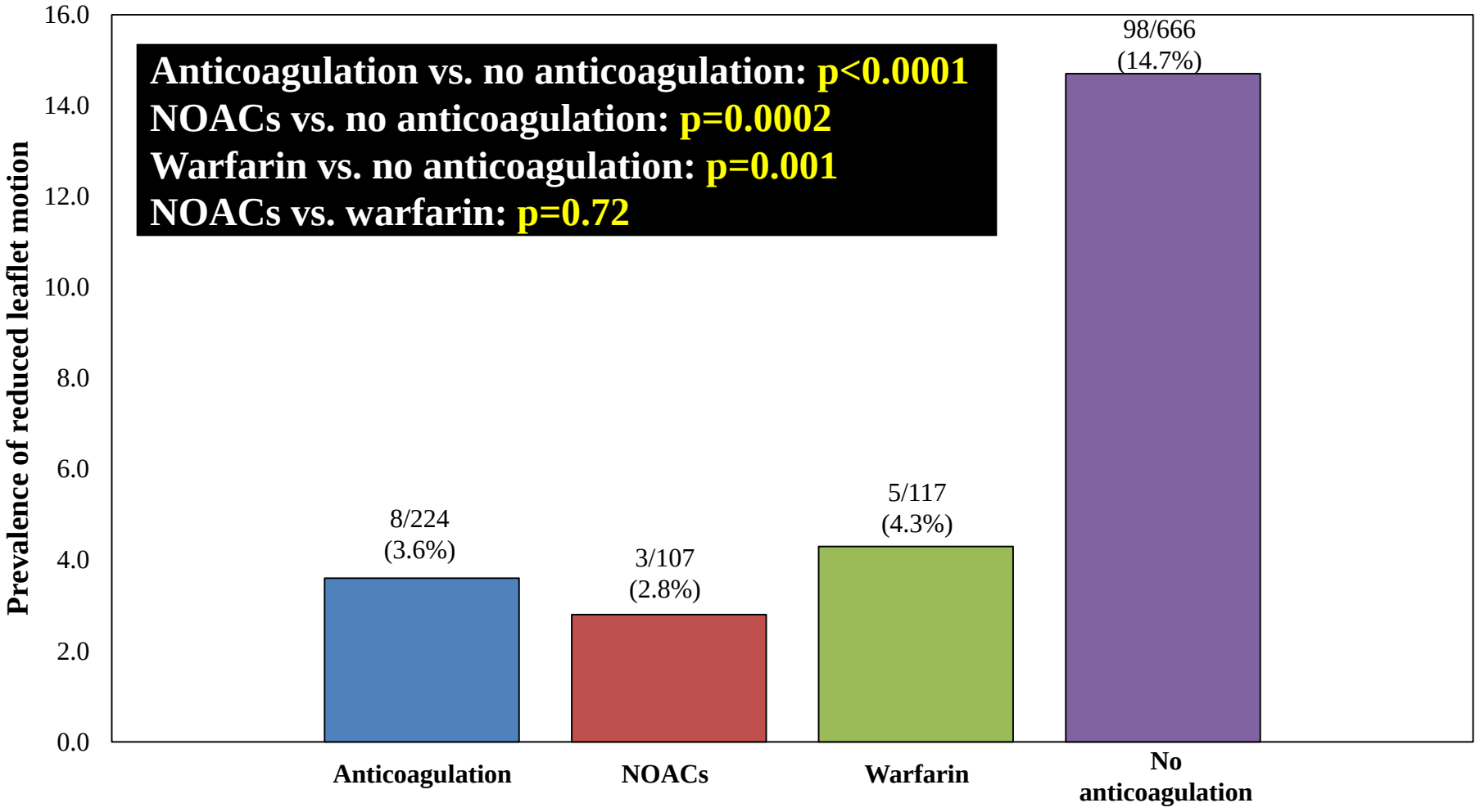
Number of leaflets affected with reduced leaflet motion

- **Surgical valves with reduced leaflet motion (n=5)**
  - 1 leaflet involved in 4 patients
  - 2 leaflets involved in 1 patient

- **Transcatheter valves with reduced leaflet motion (n=101)**
  - 1 leaflet involved in 70 patients
  - 2 leaflets involved in 25 patients
  - 3 leaflets involved in 6 patients

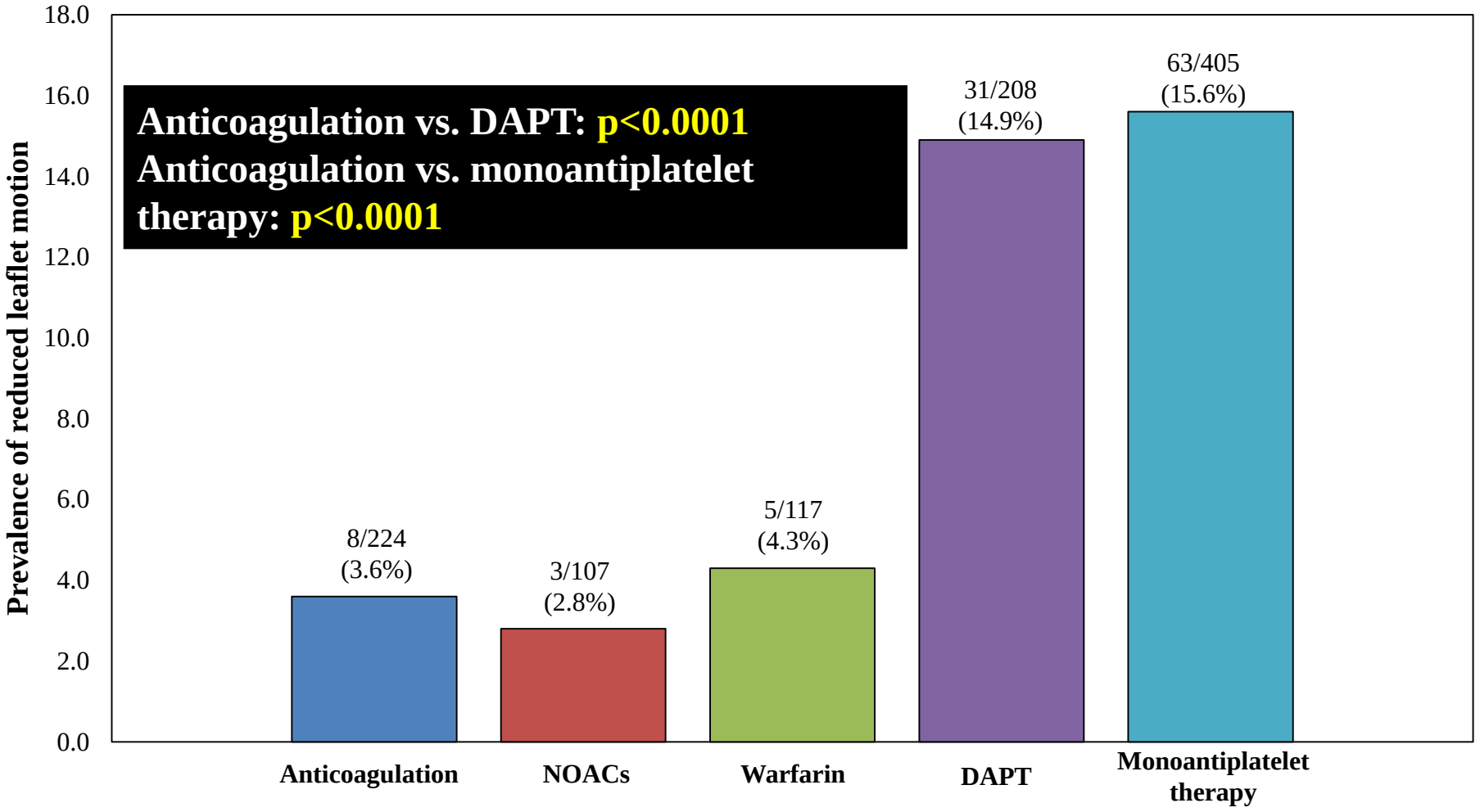
Anticoagulation and reduced leaflet motion

Anticoagulation vs. no anticoagulation



Anticoagulation and reduced leaflet motion

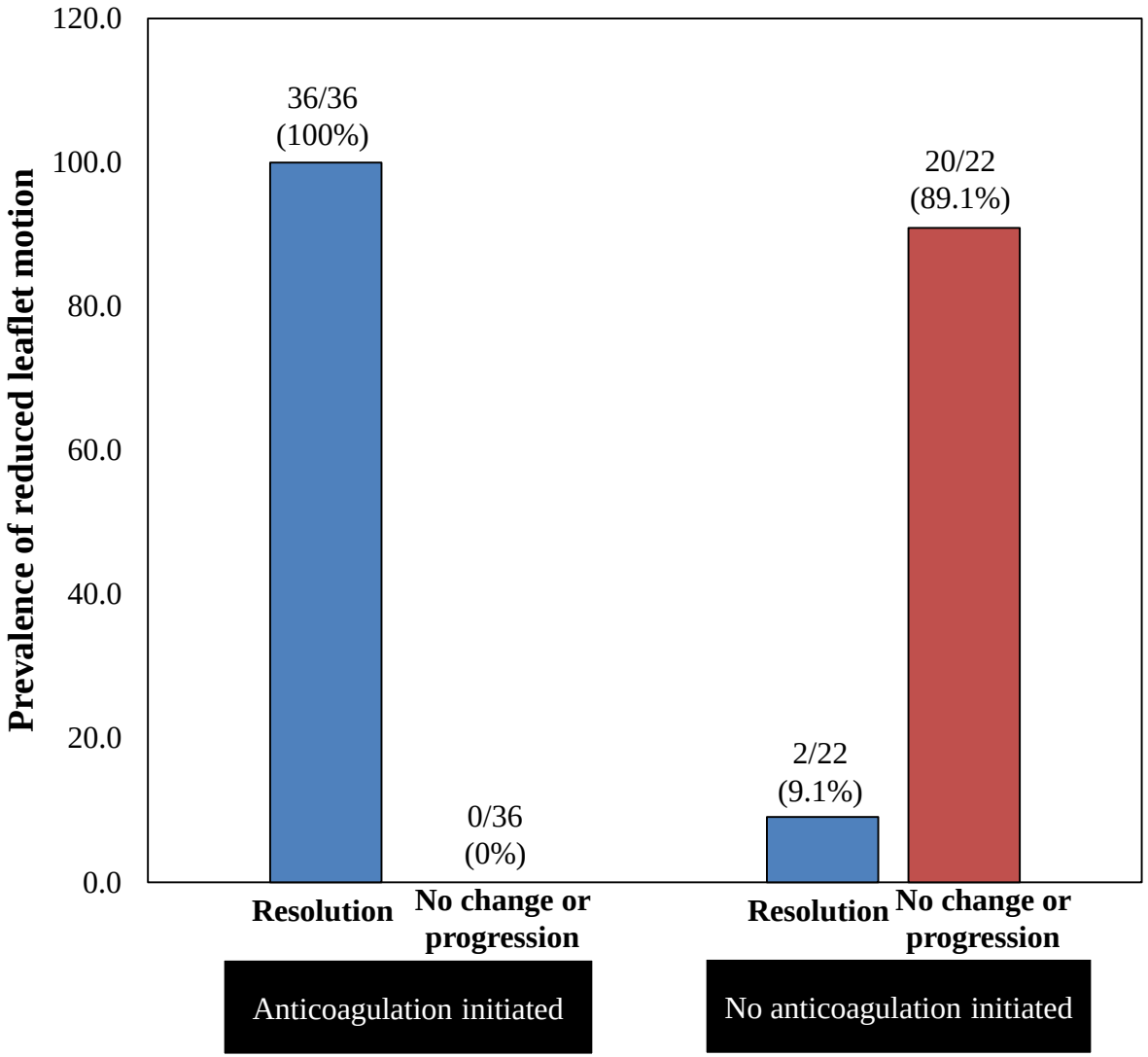
Anticoagulation vs. antiplatelet therapy



Multivariate predictors of reduced leaflet motion

	Odds ratio (95% CI)	p-value
Age	1·04 (1·01-1·07)	0·01
Ejection fraction	0·98 (0·97-1·00)	0·02
Surgical vs transcatheter valve	0·33 (0·11-0·96)	0·04
Anticoagulation	0·24 (0·10-0·58)	0·002
Time to CT	1.00 (0.98-1.02)	0.67
Atrial fibrillation	0.62 (0.31-1.23)	0.17
BMI	0.97 (0.93-1.02)	0.17

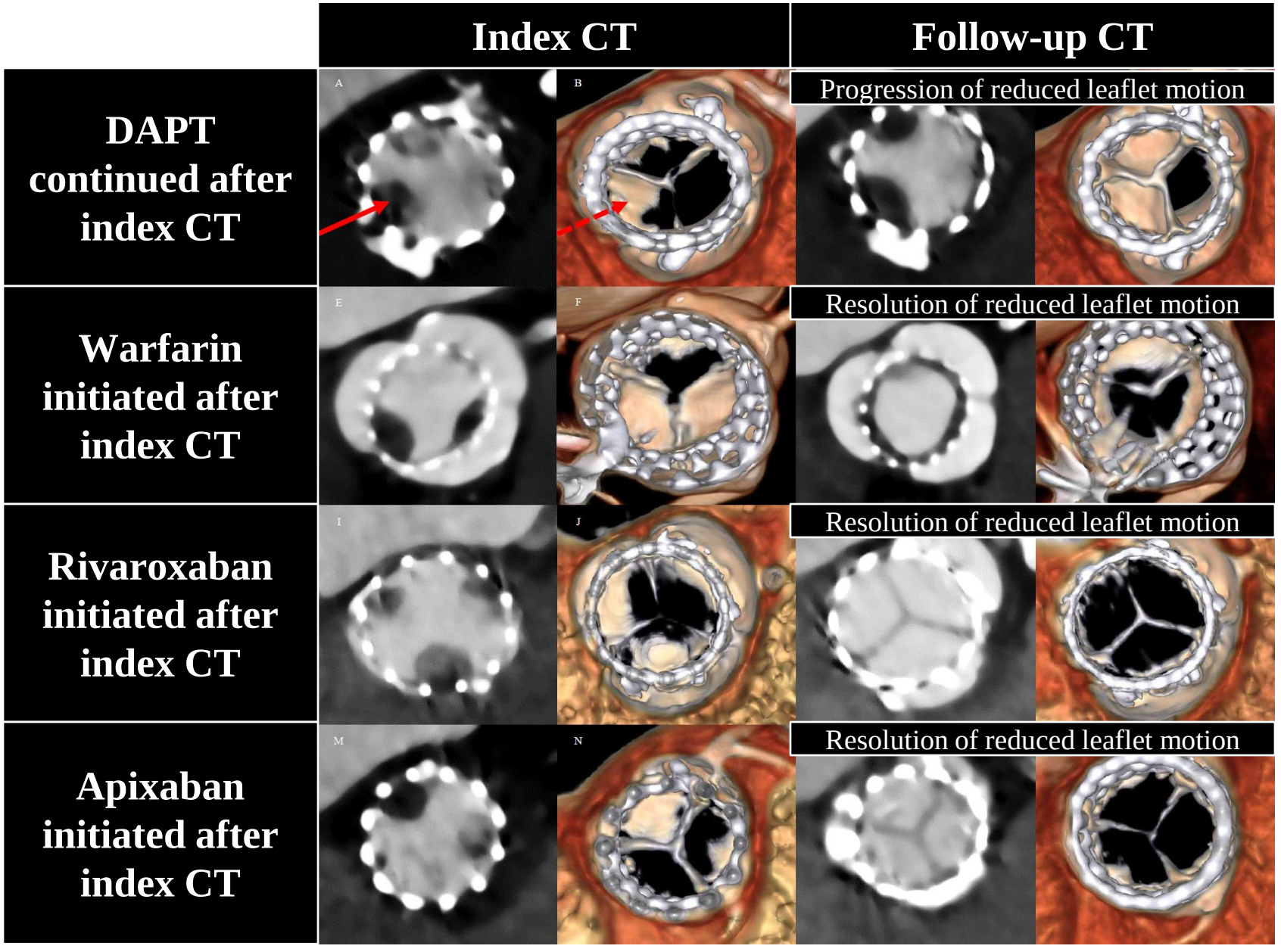
Impact of initiation of anticoagulation on reduced leaflet motion



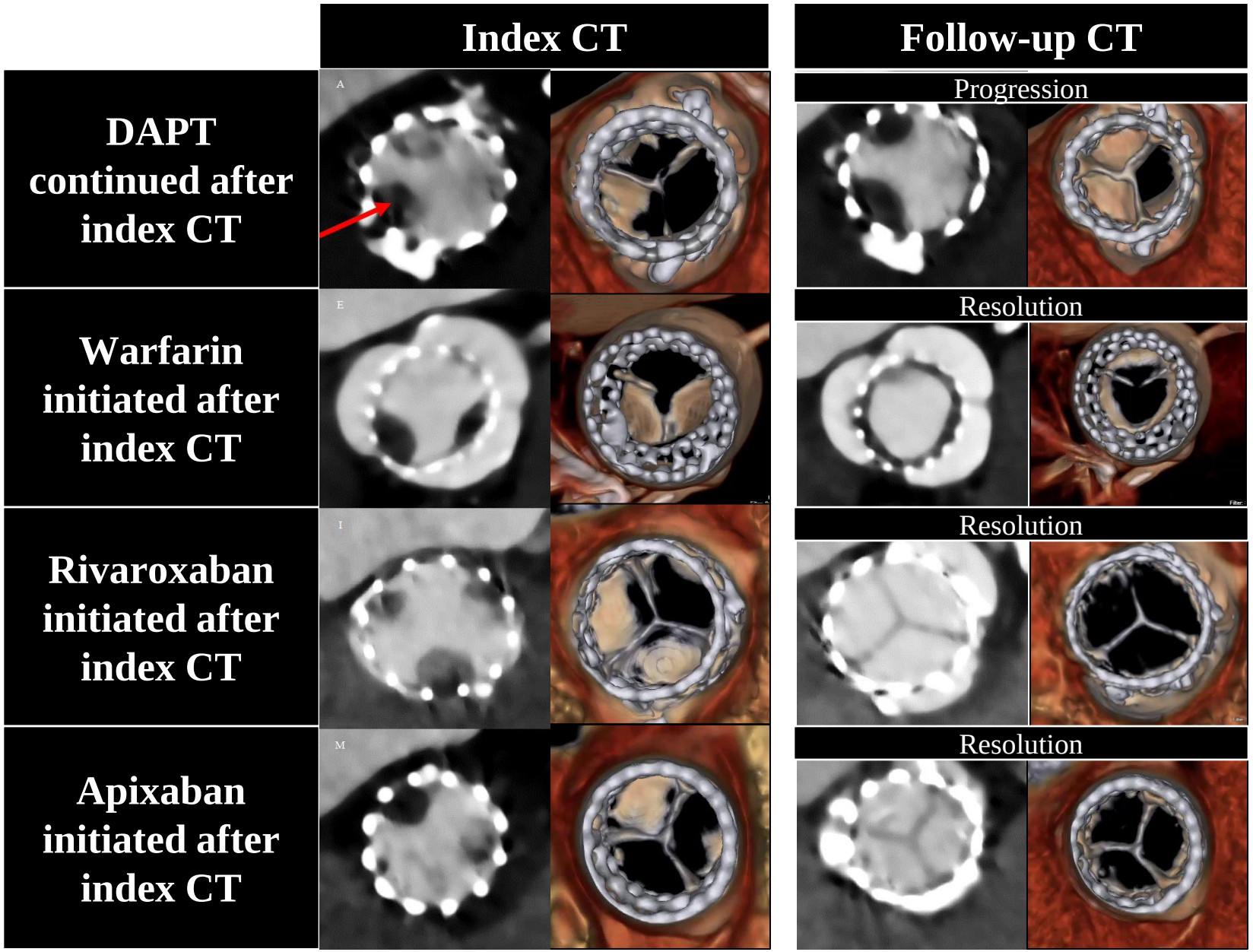
- **Resolution in 36 out of 36 patients** treated with anticoagulation (NOACs, n=12; warfarin, n=24)
- **Persistence/progression in 20 out of 22 patients** not treated with anticoagulation

P<0.0001

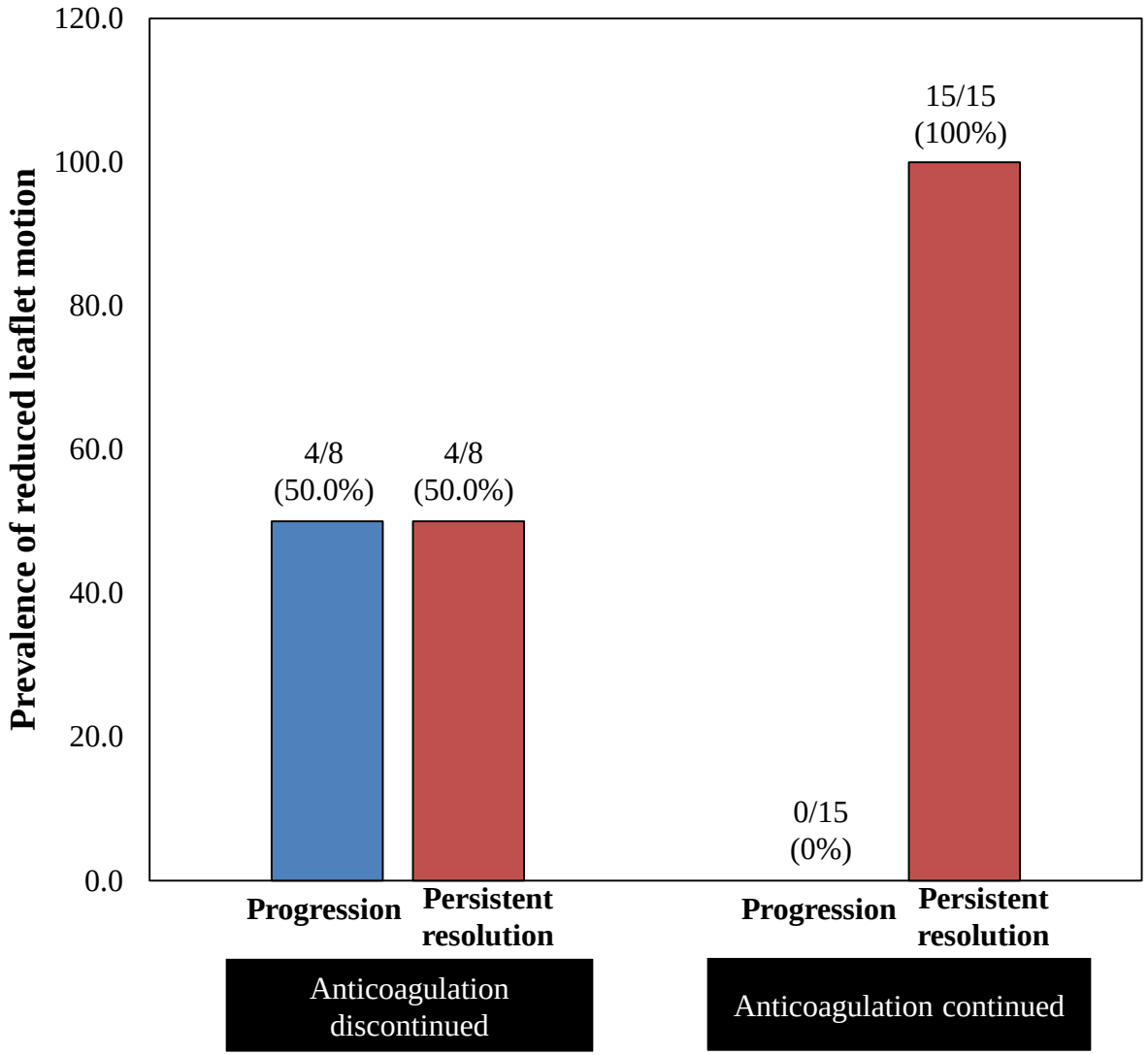
Anticoagulation vs. DAPT



Anticoagulation vs. DAPT



Impact of discontinuation of anticoagulation following resolution of reduced leaflet motion

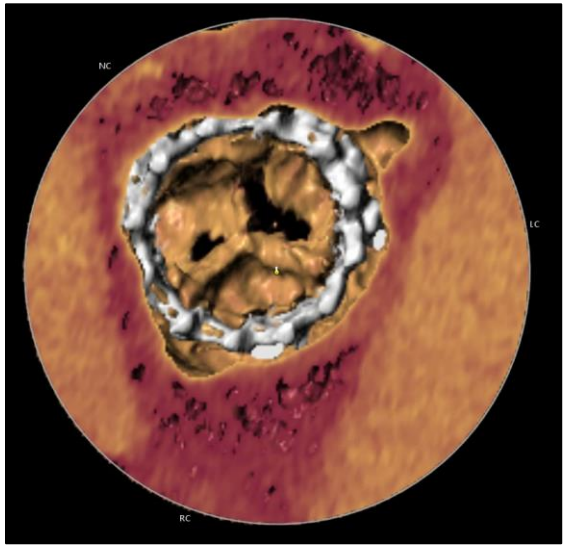


- Reduced leaflet motion **recurred in 4 out of 8 patients** in whom anticoagulation was discontinued
- Reduced leaflet motion **did not recur in the 15 patients** who were continued on anticoagulation

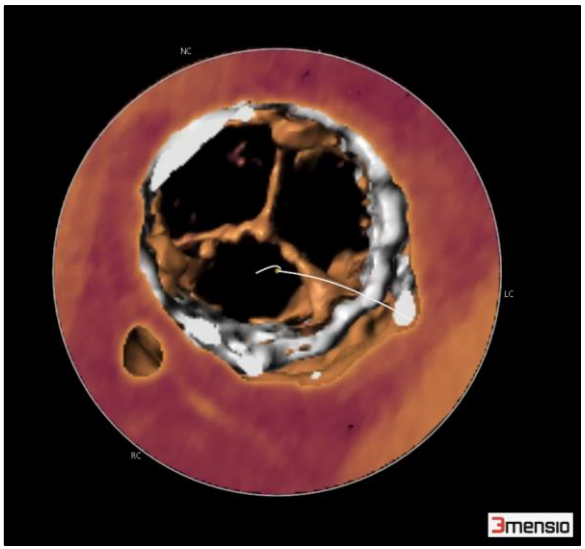
P=0.008

Recurrence of reduced leaflet motion following discontinuation of anticoagulation

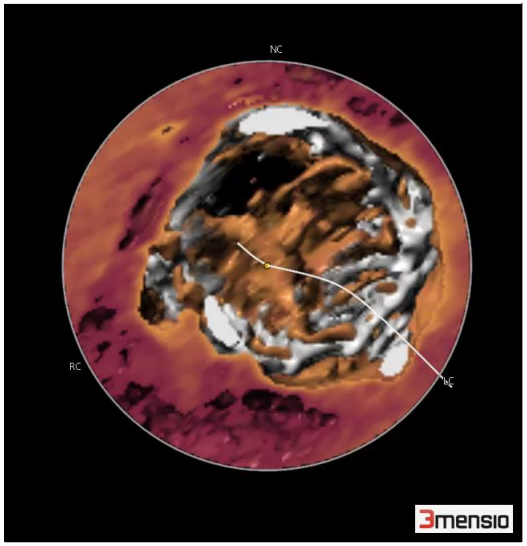
Baseline
Reduced leaflet motion



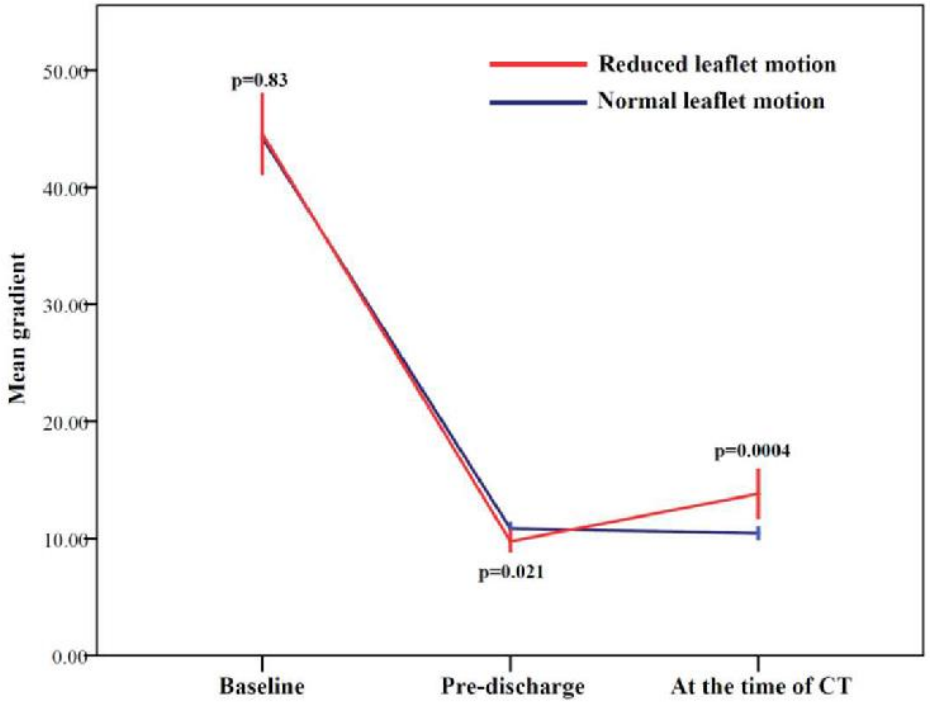
s/p Xarelto 10mg
Normal leaflet motion



Six months following discontinuation of xarelto
Reduced leaflet motion



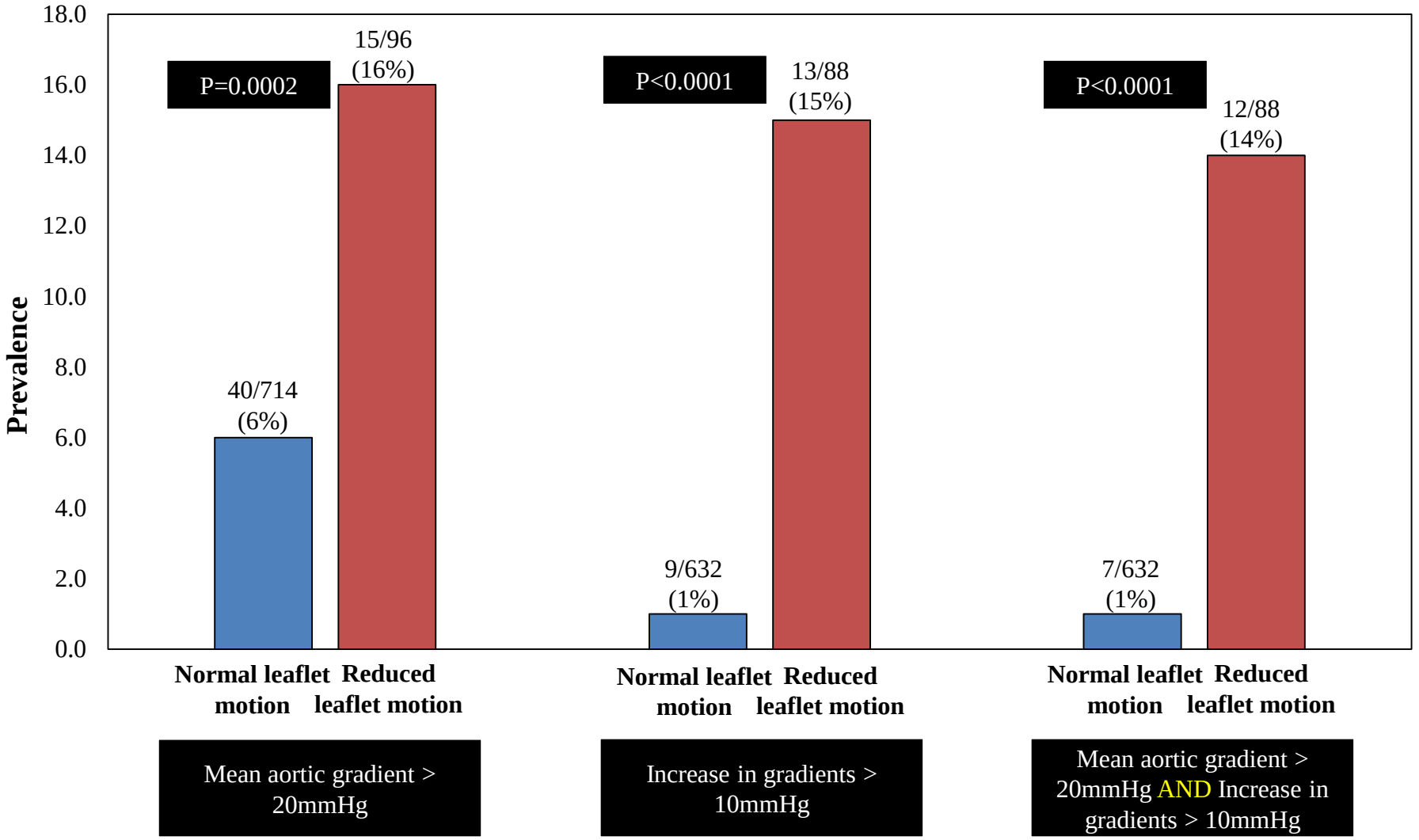
Impact of reduced leaflet motion on valve hemodynamics



Increased mean gradients at the time of CT in patients with reduced leaflet motion

13·8±10·0 mmHg vs. 10·4±6·3 mmHg, p=0.0004

Increased gradients in patients with reduced leaflet motion



Impact of reduced leaflet motion on clinical outcomes

All clinical events post-TAVR/SAVR included

No significant difference in strokes; but increased risk of TIAs and strokes/TIAs

	Normal leaflet motion (N=784)		Reduced leaflet motion (N=106)			
	n/N (%)	Rate per 100 person-years	n/N (%)	Rate per 100 person-years	Hazard ratio (95% CI)	p-value
All events						
Death	34/784 (4·3%)	2·91	4/106 (3·8%)	2·66	0·96 (0·34-2·72)	0·94
Myocardial infarction	4/784 (0·5%)	0·34	1/106 (0·9%)	0·67	1·91 (0·21-17·08)	0·56
Strokes/TIAs	27/784 (3·4%)	2·36	11/106 (10·4%)	7·85	3·27 (1·62-6·59)	0·001
All strokes*	22/784 (2·8%)	1·92	6/106 (5·7%)	4·12	2·13 (0·86-5·25)	0·10
Ischemic strokes	21/784 (2·7%)	1·83	6/106 (5·7%)	4·12	2·23 (0·90-5·53)	0·08
TIAs	7/784 (0·9%)	0·60	6/106 (5·7%)	4·18	7·02 (2·35-20·91)	0·0005

TIA=Transient ischemic attack

* All strokes include hemorrhagic and ischemic strokes

Impact of reduced leaflet motion on clinical outcomes

Only non-procedural events (>72 hours post-TAVR/SAVR) included

No significant difference in strokes; but increased risk of TIAs and strokes/TIAs

	Normal leaflet motion (N=784)		Reduced leaflet motion (N=106)			
	n/N (%)	Rate per 100 person-years	n/N (%)	Rate per 100 person-years	Hazard ratio (95% CI)	p-value
Non-procedural events						
Death	34/784 (4·3%)	2·91	4/106 (3·8%)	2·66	0·96 (0·34-2·72)	0·94
Myocardial infarction	4/784 (0·5%)	0·34	1/106 (0·9%)	0·67	1·91 (0·21-17·08)	0·56
Strokes/TIAs	20/784 (2·6%)	1·75	8/106 (7·6%)	5·71	3·30 (1·45-7·50)	0·004
All strokes*	15/784 (1·9%)	1·31	4/106 (3·8%)	2·75	2·14 (0·71-6·44)	0·18
Ischemic strokes	14/784 (1·8%)	1·22	4/106 (3·8%)	2·75	2·29 (0·75-6·97)	0·14
TIAs	7/784 (0·9%)	0·60	5/106 (4·7%)	3·48	5·89 (1·87-18·60)	0·002

TIA=Transient ischemic attack

* All strokes include hemorrhagic and ischemic strokes

Impact of reduced leaflet motion on clinical outcomes

Only clinical events occurring post-CT included

No significant difference in strokes; but increased risk of TIAs and strokes/TIAs

	Normal leaflet motion (N=784)		Reduced leaflet motion (N=106)			
	n/N (%)	Rate per 100 person-years	n/N (%)	Rate per 100 person-years	Hazard ratio (95% CI)	p-value
Post-CT events						
Death	34/774 (4·4%)	5·08	4/105 (3·8%)	4·61	0·92 (0·33-2·60)	0·88
Myocardial infarction	2/772 (0·26%)	0·30	0/104 (0%)	NA	NA	NA
Post-CT strokes/TIAs	10/757 (1·3%)	1·53	4/98 (4·1%)	5·15	3·45 (1·08-11·03)	0·04
All strokes*	7/759 (0·9%)	1·06	2/101 (2·0%)	2·42	2·41 (0·50-11·61)	0·27
Ischemic strokes	6/759 (0·8%)	0·91	2/101 (2·0%)	2·42	2·81 (0·57-13·92)	0·21
TIAs	5/772 (0·7%)	0·75	3/102 (2·9%)	3·73	5·02 (1·20-21·10)	0·03

TIA=Transient ischemic attack

* All strokes include hemorrhagic and ischemic strokes

Study limitations

- This is an observational study and the impact of unmeasured confounders on the results of the study cannot be excluded.

- Although our study reveals an association between stroke/TIA and reduced leaflet motion, the temporal separation between the clinical events and the CT scans makes it difficult to state leaflet thrombosis as the definitive cause for neurologic events.

- Time from AVR to CT was different between TAVR and SAVR cohorts; however, time to CT was not an independent predictor of subclinical leaflet thrombosis in multivariate analysis.

Conclusions

- In a heterogeneous cohort of aortic bioprosthetic valves, the reduced leaflet motion occurred 12 % of the time on 4D CT.

- Patients undergoing SAVR, compared with TAVR, had lower incidence of reduced leaflet motion (3.6% vs. 12%; $p<0.04$). However, patients undergoing SAVR were different than TAVR reflecting contemporary practice with lower age and fewer comorbidities.

- Anticoagulation with both warfarin and NOACs ***and not DAPT which is the standard of care*** were effective in prevention and treatment of reduced leaflet motion.

- Majority of cases of subclinical leaflet thrombosis diagnosed by 4D CT are hemodynamically silent and hence missed by TTE

Conclusions, *contd.*

- Patients with subclinical leaflet thrombosis had a small but significant increase in transvalvular gradients compared to patients without subclinical leaflet thrombosis

- A greater proportion of patients with subclinical leaflet thrombosis (15% vs. 1%) had hemodynamically significant increase in gradients (aortic valve gradients>20mmHg and increase in aortic valve gradients>10mmHg).

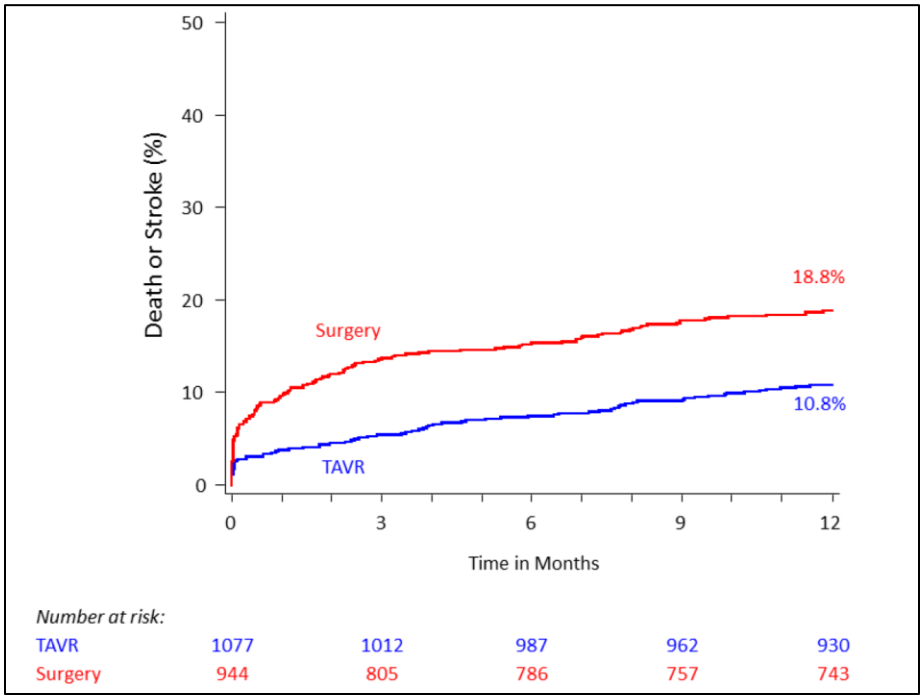
- While the death, MI and stroke rates were not significantly different between the 2 groups, subclinical leaflet thrombosis was associated with increased rates of TIAs and strokes/TIAs.

Clinical implications

- The imaging findings in our analysis question the current standard of care (dual antiplatelet therapy post-TAVR); thus DAPT can be considered dispensable in the appropriate clinical setting. Our findings raise the issue if anticoagulation is more appropriate in certain patients.
- Our data call for clinical trials of routine CT imaging and anticoagulation as TAVR moves into lower risk patients and for the first time provide evidence on the efficacy of NOACs on bioprosthetic valve thrombosis
- In the appropriate clinical setting such as TIAs, stroke, new onset heart failure; or even small increase in gradients post-procedure should lead to vigilance and CT imaging.
- The reduced leaflet motion observed on CT secondary to leaflet thrombosis and increase in gradients may provide insights into a preventable mechanism of structural valve deteriorartion in some patients

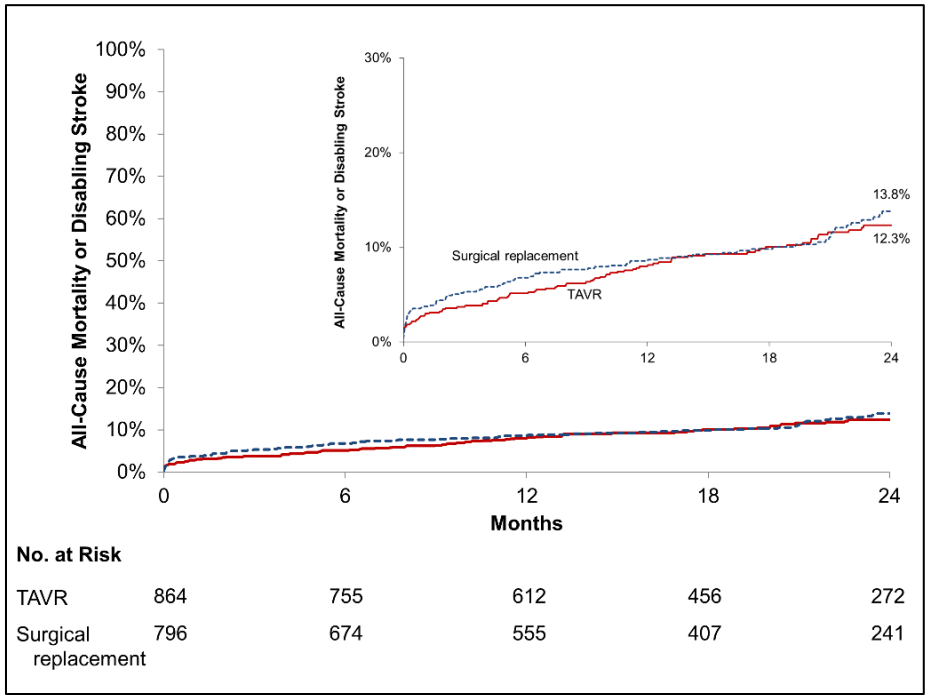
The choice of therapy (SAVR or TAVR) and device is best guided by clinical outcomes data in clinical trials rather than a single imaging finding such as subclinical leaflet thrombosis

Lower 1-year death/stroke rates with Sapien 3, compared with surgery



Thourani V. et al. Lancet 2015

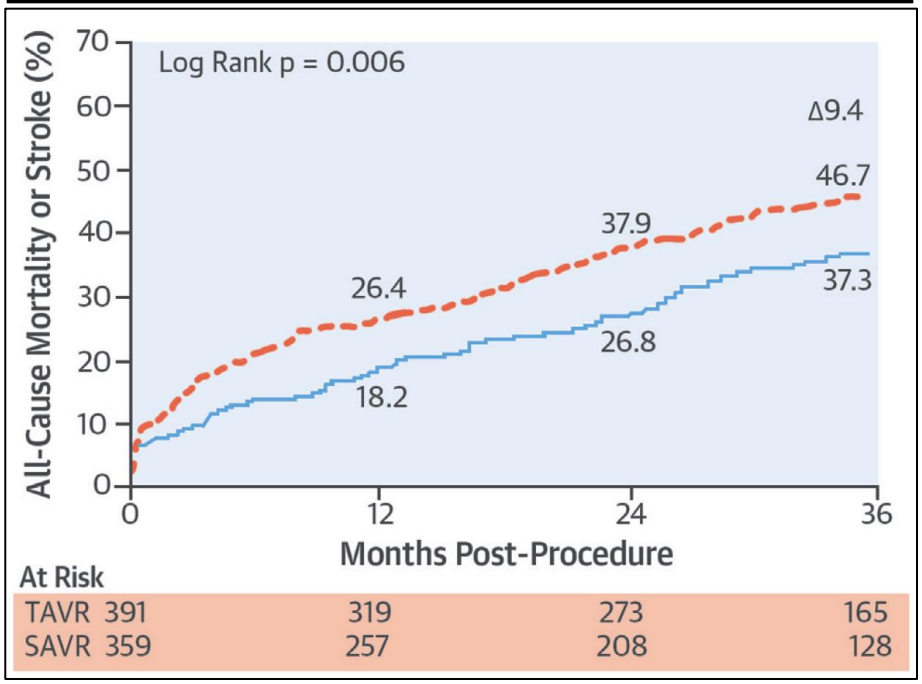
Similar 2-year death/stroke rates with CoreValve, compared with surgery



Reardon M. et al. NEJM 2017

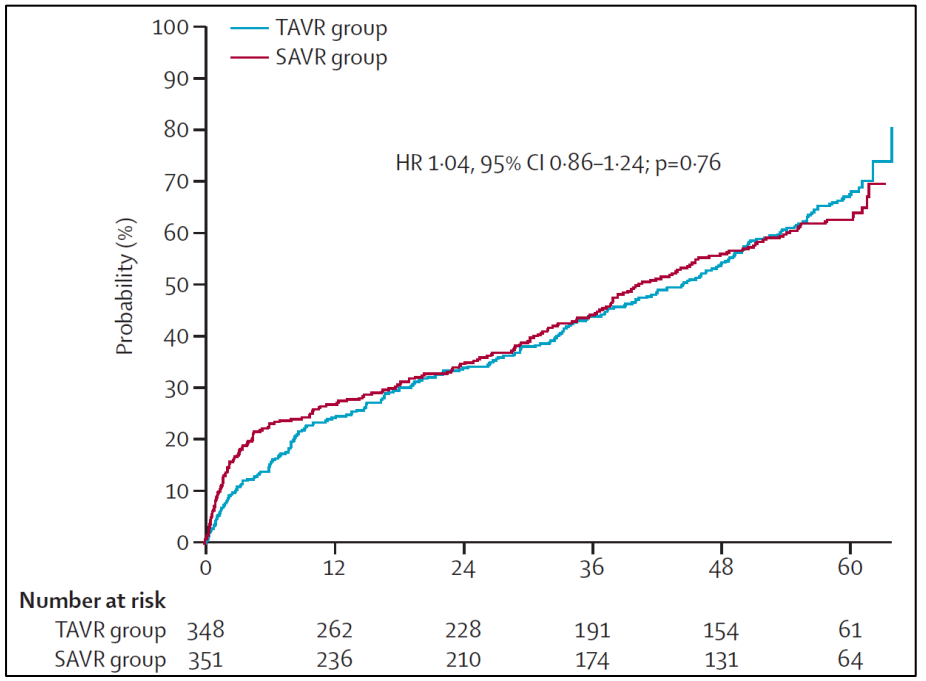
Despite excellent clinical outcomes of newer generation valves our study findings can help further optimize adjunctive pharmacotherapy which may result in further improvements.

Lower 3-year death/stroke rates with CoreValve, compared with surgery



Deeb M. et al. JACC 2016

Similar 5-year death rates with Edwards-SAPIEN, compared with surgery



Mack M. et al. Lancet 2015

Subclinical leaflet thrombosis in surgical and transcatheter bioprosthetic aortic valves: an observational study

*Tarun Chakravarty, Lars Søndergaard, John Friedman, Ole De Backer, Daniel Berman, Klaus F Kofoed, Hasan Jilaihawi, Takahiro Shiota, Yigal Abramowitz, Troels H Jørgensen, Tanya Rami, Sharjeel Israr, Gregory Fontana, Martina de Knegt, Andreas Fuchs, Patrick Lyden, Alfredo Trento, Deepak L Bhatt, Martin B Leon, Raj R Makkar, on behalf of the RESOLVE and SAVORY Investigators**

Lancet online March 19, 2017

Research in context

Evidence before this study

We searched MEDLINE on Feb 1, 2017, for articles published in English, with the search terms "bioprosthetic valve thrombosis", "transcatheter aortic valve thrombosis", "subclinical leaflet thrombosis", "hypoattenuating leaflet thickening", and "TAVR thrombosis". Although symptomatic thrombosis represents the extreme end of the spectrum of bioprosthetic aortic valve thrombosis and is probably under-reported (prevalence of 1–2%), been attributed to subclinical leaflet thrombosis in previously reported series. The published series have several limitations, including absence of complete clinical follow-up, no core laboratory assessment of transthoracic echocardiograms, no information about differences in the prevalence and severity of subclinical leaflet thrombosis between transcatheter and surgical valves, no adjudication of neurological events, and no information about the efficacy of novel oral anticoagulants (NOACs).

Added value of this study

We report, to our knowledge, the largest study to date of 931 patients who had CT scans done after surgical or transcatheter aortic valve replacement (TAVR) to assess reduced leaflet motion and its effect on clinical outcomes. This study is the first, to our knowledge, to report differences in subclinical leaflet thrombosis between surgical and transcatheter aortic valves. Findings from this study are also the first, to our knowledge, to show the potential efficacy of NOACs in the prevention and treatment of subclinical leaflet thrombosis in bioprosthetic aortic valves. The frequency and severity of subclinical leaflet thrombosis was lower in surgical than in transcatheter aortic valves. Patients with reduced leaflet motion had a small, but significant, increase in valve gradients. Anticoagulation was better than dual antiplatelet therapy (DAPT; transient ischaemic attacks and strokes or transient ischaemic attacks associated with reduced leaflet motion, although the rates of strokes were not significantly different.

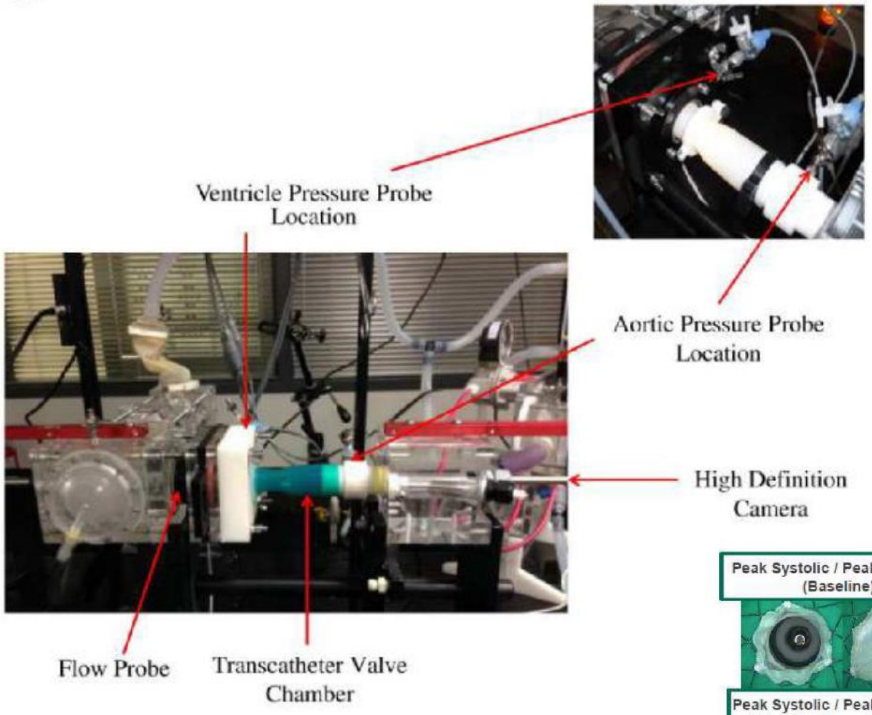
Implications of all the available evidence

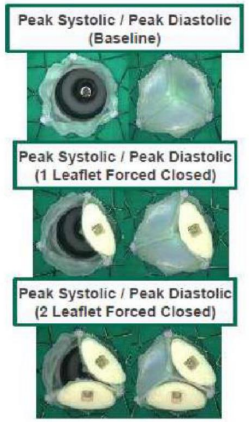
Our findings question the guidelines recommending DAPT after TAVR and raise the issue of whether or not warfarin or NOACs are more appropriate in certain patients than is DAPT.
The risk-benefit profile of anticoagulation will be established in future clinical trials. Despite excellent outcomes after TAVR with the new-generation valves, room might exist for further improvement in outcomes through an understanding of the predictors of reduced leaflet motion and consideration of a short course of anticoagulation if findings from ongoing randomised trials substantiate these existing findings.

Backup slides

Pulse duplicator model to evaluate the effect of leaflet motion on valve gradients

Gradients not affected with immobilization of 1-2 leaflets





Valve Size (mm)	Leaflet(s) Forced Closed	Mean Pressure Gradient (mmHg)	Effective orifice area (cm^2)
23	0	4.0	2.69
23	1	7.9	1.84
23	2	42.3	0.77
25	0	3.3	2.86
25	1	5.3	2.25
25	2	21.1	1.05
27	0	3.2	3.14
27	1	5.7	2.19
27	2	20.4	1.09
29	0	2.1	3.49
29	1	3.1	3.25

Prevalence of reduced leaflet motion in individual valve types

	Frequency N=106
Transcatheter valves	**101/752 (13·4%)**
Edwards	63/453 (13·9%)
Edwards-Sapien	1/22 (4·6%)
Sapien-XT	12/122 (9·8%)
Sapien-3	50/309 (16·2%)
Evolut/CoreValve	9/145 (6·2%)
CoreValve	3/70 (4·3%)
Evolut	6/75 (8·0%)
Lotus	12/83 (14·5%)
Portico	15/50 (30·0%)
Direct flow	0/6 (0%)
Centera	1/7 (14·3%)
Symetis	1/8 (12·5%)
Surgical valves	**5/138 (3·6%)**
Epic	0/16 (0%)
Freestyle	0/2 (0%)
Magna	4/37 (10·8%)
Mitroflow	0/11 (0%)
Perimount	1/39 (2·6%)
Trifecta	0/33 (0%)